Title

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Journal

Journal of Periodontology, 94(4)

ISSN

0022-3492

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Publication Date

2023-04-01

DOI

10.1002/jper.22-0254

Peer reviewed

Better Living Through Chemistry? A Randomized, Double-blind Controlled Study Evaluating the Efficacy of Plaque Control and Gingival Health Impacts of a Novel Stannous Fluoride-Containing Gel.

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Word Count: 3856

Figures: 2

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/JPER.11016.

Tables: 2

References: 58

Running Title: Novel fluoride dental gel reduces plaque and gingival inflammation

One Sentence Summary: The novel dental gel demonstrated significant improvements in clinical parameters associated with gingivitis compared to a commercially available sodium fluoride dentifrice

Key Words: Gingivitis, Oral Hygiene, Plaque Control, Prevention, Inflammation

Abstract:

Background:

Gingivitis is a non-specific inflammatory lesion in response to accumulation of oral biofilm and is a necessary precursor to periodontitis. Enhanced oral hygiene practices are necessary to reverse gingivitis and a dentifrice that could provide significant clinical reductions in plaque accumulation and gingival inflammation would be desirable to treat gingivitis and potentially prevent progression to periodontitis. This clinical study aimed to investigate the effect of a novel stannous fluoride-containing dentifrice with 2.6% ethylenediamine tetra acetic acid (EDTA) as an anti-tartar agent to reduce plaque index and gingival index over a 3-month study period.

Methods:

This double-blind, randomized controlled clinical study evaluated plaque, gingival inflammation, and sulcular bleeding in patients using either a novel dental gel containing 0.454% stannous fluoride and 2.6% EDTA or a dentifrice with 0.24% sodium fluoride. 60 subjects participated over a 3-month period. Co-primary endpoints were improvements in plaque index (PI) and modified gingival index (mGI) from baseline values. No professional cleaning was performed during the study period.

Results:

All subjects in the study demonstrated statistically significant improvements in all measures of oral hygiene over the 3-month study period. Subjects using the novel dental gel showed statistically significantly greater reductions in PI (ΔPI) [(-1.43 $\pm$ 0.34; -0.49 $\pm$ 0.13)($p < 0.00001$)], mGI (ΔmGI) [(-1.11 $\pm$ 0.22; -0.16 $\pm$ 0.12)($p < 0.00001$)], and modified sulcular bleeding index (ΔmSBI) [(-1.15 $\pm$ 0.18; -0.20 $\pm$ 0.07)($p < 0.00001$)].

Conclusion:

The novel dental gel demonstrated significant improvements in clinical parameters associated with gingivitis compared to a commercially available sodium fluoride dentifrice.

Introduction:

Dental biofilm contains over 800 species of microbes that include both non-disease and disease-producing organisms.[1] In health, these organisms co-exist in a symbiotic state, however, if a dysbiosis of the oral microbiome occurs, the pathogenic microbes take over and play a role in the initiation of both dental caries and periodontal disease, the two most prevalent oral diseases.[2] Dental biofilm is a heterogenous population of microorganisms within a polysaccharide extracellular matrix that is deposited on surfaces throughout the mouth starting immediately after its removal.[3] Biofilm deposits typically begin at the gingival margin and progress both coronally and apically into the subgingival environment and as the biofilm ages, the microorganisms within the biofilm become increasingly virulent resulting in dysbiotic biofilms that are associated with oral disease.[4,5] Bacteria and their byproducts within such biofilms can initiate host immuno-inflammatory responses that result in local inflammation and, if the inflammatory response is not addressed, the irreversible destruction of the periodontal attachment apparatus and in the presence of carbohydrate fuel are also responsible for local shifts in pH that can result in dental caries.[4,5]

As an integral part of the prevention and treatment of caries and periodontal diseases, patients become co-practitioners with their oral health providers and their sustained daily maintenance of oral hygiene becomes critical to the success of professional oral health interventions. However, patient levels of home care vary considerably and are often suboptimal. Despite recommendations from the ADA that individuals brush for two minutes twice daily,[6] the average individual performs 45-70 seconds of toothbrushing daily.[7] Additionally, patient compliance with regular daily use of dental floss has been estimated to be as low as 2%.[8] Given the importance of regular biofilm removal and because biofilm is a critical etiologic factor for both periodontal diseases and dental caries, the effective and regular removal of dental biofilm and the reduction or elimination of dysbiotic pathogens is critical to achieving optimal oral health.[9] The success of advanced periodontal and restorative therapies is dependent upon removal of biofilm and elimination of oral pathogens associated with the tooth surfaces, periodontal tissues, mucosal surfaces, the tongue dorsum, and other niches within the oral cavity.[10] Furthermore, the long-term maintenance of the results of periodontal and restorative therapies rely upon a patient's ability to achieve prolonged adequate levels of oral hygiene and consistent maintenance and examination visits with a dental professional.[10] This then highlights the crucial role of the patient as a co-practitioner in the prevention and treatment of periodontitis and gingivitis and the establishment of periodontal health.

Both dental caries and periodontal diseases are extremely prevalent in the adult US population. Untreated tooth decay affects 32% of US adults ages 20-44 years[11] and 92% of dentate adults have

decay in a permanent tooth.[12] Further, the average adult has 3.28 decayed, missing, or filled teeth.[12] Further, the prevalence of periodontitis has been estimated to be over 47% of U.S. adults over 30 years of age.[13] Periodontitis is extremely prevalent and after initiation by bacteria and bacterial virulence factors, disease progression and tissue destruction occurs through host-mediated inflammatory pathways,[14] which may vary based upon genetic and other risk factors.[15-17] The result is a biofilm-initiated, chronic immuno-inflammatory disease that may pose a significant systemic burden for individuals.[18] Patients' quality of life is negatively affected by poor oral health, including periodontal disease, dental caries and edentulism.[19,20]

Given the demonstrated importance of biofilm disruption for the prevention and treatment of dental caries and periodontal diseases, the use of chemotherapeutic agents within dentifrices for improved patient-delivered oral hygiene have been utilized to enhance biofilm removal and reduce caries and gingival inflammation. Limitations to existing anti-plaque therapies include reported taste alteration, tooth structure staining, dental abrasion, dentinal sensitivity, and reactive gingival lesions.[21] Previous studies have demonstrated the efficacy of a dental gel with 2.6% ethylenediamine tetra acetic acid (EDTA) as an anti-tartar agent in reducing oral plaque deposit, gingival inflammation, and probing depths with minimal patient-reported side effects or impact upon tooth surface microarchitecture and microhardness.[22-27] These previous investigations of 2.6% EDTA containing dentifrice lacked the inclusion of fluoride in the formulation.

This study aimed to evaluate the safety and efficacy of a novel dentifrice containing 0.454% stannous fluoride and 2.6% EDTA (Livionex, Los Gatos, CA) when compared to a control dentifrice containing 0.24% sodium fluoride (Church & Dwight, Ewing, NJ) without additional provider-delivered care over a 3-month period.

Materials and Methods:

Study design and participants

This single-center, double-blind, randomized controlled clinical study was performed to evaluate plaque, gingival inflammation, and sulcular bleeding over a 3-month period. This project was performed at the University of California Irvine and approved by the University Institutional Review Board (IRB) (Protocol #2013-9778, #2002-2805, and #881) and registered at ClinicalTrials.gov (#NCT02271815). All procedures were conducted in accordance with the Helsinki Declaration of 1975, as updated in 2013.[28] No substantial changes were made to the protocol and/or study design after commencement of the study.

Sixty participants were recruited to participate in this study from University staff, students, faculty, local community, local dentist offices and low-cost dental clinics. Males or females $\geq$ 18 years of age with a minimum of 25 teeth were included in this study. Inclusion criteria were as follows: 1)

baseline mean whole-mouth plaque index ≥ 2.0[29], 2) baseline mean whole-mouth modified gingival index ≥ 2.0[29], 3) baseline mean whole-mouth modified sulcular index ≥ 1.0[30], 4) ability to provide written informed consent and comply with study visits as described in the protocol, and 5) availability for follow up via telephone. Exclusion criteria were as follows: 1) pregnant females, 2) participation in another clinical trial within 30 days of baseline, 3) urgent dental needs, 4) history of adverse effects after use of oral care products, including dentifrices and mouth rinses, and/or allergy to personal care/consumer products or their ingredients, 5) unable or unwilling to sign the informed consent form, 6) diagnosis of immune deficiency diseases (e.g. HIV/AIDS, poorly controlled diabetes mellitus), 7) use of anti-TNF- α medication, anti-inflammatory drugs, or immune suppressants, 8) use of systemic antibiotics within 3 months prior to baseline, 9) other systemic conditions or medication use at baseline that the principal investigator adjudicated may affect the patient's ability to participate with study requirements (including the use of local antibiotics for oral diseases/conditions), and 10) cigarette smoking. After eligibility was determined based upon inclusion/exclusion criteria, participants were randomly assigned by a computer-generated block randomization in a 1:1 ratio to receive either the test or control dentifrice. Recruitment was accomplished on a rolling basis beginning in April 2021 and all study visits were completed by a single examiner by December 2021.

Study products and interventions

Both study participants and examiner were blinded to randomization throughout the study duration. No professional dental cleaning was performed during the study duration. Subjects were provided with a new manual toothbrush (Oral-B, Pro-Flex, Procter & Gamble Company, Cincinnati, OH) and were given standardized instructions using the tell-show-do method in sulcular brushing techniques by the study examiner with 25 years of experience as a dentist. All study products were packaged in uniform, plain white numbered tubes.

The study products included:

1. Test dentifrice: a novel dentifrice containing 0.454% stannous fluoride with 2.6% EDTA as a tartar control agent (LivFresh Dental Gel SF, Livionex Inc., Los Gatos, CA).

2. Control dentifrice: a commercially available dentifrice with 0.24% sodium fluoride (AIM multi-benefit cavity protection gel toothpaste, Church & Dwight, Ewing, NJ).

Participants were instructed to brush with the study material twice daily for two minutes using a pea-sized amount of the provided dentifrice. All packaging was masked to facilitate participant blinding. Subjects were asked not to use any another oral hygiene products, including interproximal cleaning devices throughout the study duration. Compliance was confirmed with once-weekly telephone contact. Subjects were required to return used dentifrice tubes at monthly visits and tubes were weighed to measure compliance. Dentifrice tubes were replenished at monthly visits. No professional dental cleaning was performed during the course of the study. Each subject received an incentive of $25 per visit in accordance with the IRB-approved protocol.

Data Collection

Age, gender, and race/ethnicity were obtained for all subjects enrolled in the study. Brushing protocols with the test and control dentifrice were initiated at the baseline (day 0) visit when subjects were enrolled in the study. Study duration was 3 months (90 ± 5 days). Clinical outcomes were assessed at baseline (day 0) and Visit 2 (90 ± 5 days). The following clinical variables were recorded at both visits by the same blinded, calibrated, experienced study dentist. Clinical measurement calibration takes place on a quarterly basis with a minimum of 90% accuracy.

1. Plaque Index (PI): Quigley Hein with Turesky modification[28]
2. Modified Gingival Index (mGI): Silness and Löe gingival index without the bleeding on probing component[28]
3. Modified Sulcus Bleeding Index (mSBI)[29]

Furthermore, patient-reported dentifrice efficacy and tolerance were reported through weekly telephone calls.

The co-primary efficacy endpoints were improvement in mean PI and mGI at 3 months as compared to baseline. Secondary efficacy endpoints included improvements mSBI. The prospective study objective was to compare the relative efficacy of the test dentifrice and the positive control dentifrice. Safety was monitored throughout the study by assessing the incidence, timing, and severity of adverse events (AEs) as well as by overall assessment of oral health by the examiner at the final study visit. Subjects were also provided with a direct telephone number to contact in the case of any AEs.

Sample Size and Statistical Analysis

This was a superiority study using a standard fluoride toothpaste control (commercially available Aim Multi-Benefit Cavity Protection Gel Toothpaste with Sodium Fluoride). Sample size calculations were based upon prior studies conducted by Livionex using a fluoride toothpaste as control. For a superiority study, a standard deviation of 0.257 for Gingival Index, a superiority limit of 0.22 (10% of the final GI value of 2.2) was used. Using a significance level (alpha) of 0.05 (5%) and a Power (1-beta) of 0.8 (80%), the necessary sample size required is 15 per group or a total size of 30. For an abundance of caution, and in order to meet ADA Seal of Acceptance requirements, the study enrolled 30 subjects per group, or a total size of 60 subjects, randomized in a 1:1 ratio.

The differences between the outcomes were tested using a two tailed Student's T test and statistical significance was determined by $p < 0.05$. Microsoft Excel 365 (Microsoft Corporation; Redmont, WA) was used to tabulate data and calculate descriptive statistics (i.e., means and standard deviations). Statistical analysis using online statistical calculators available at https://www.quantitativeskills.com/sisa/index.htm

Results:

All enrolled subjects reported completion of the study in full compliance with the protocol during all telephone contacts and in-person dental visits. No adverse events were reported. A summary of participant demographics is included in Table 1. Study participants ranged from 19 – 33 years old with a mean age of 22.5 years. The study population was 47% female and 53% male. No statistically significant differences in age, gender, and/or race/ethnicity were seen between groups at baseline. No adverse effects were reported regarding the use of either dentifrice during the study period. Study findings are summarized in Table 2 and Figures 1 and 2.

Plaque Index

PI was reported as whole-mouth mean values using the Quigley Hein plaque index with Turesky modification.[29] The findings related to PI at baseline and 3-months are reported in Table 2. At baseline the test dentifrice group had a statistically significant greater whole mouth mean plaque score when compared to the control dentifrice group [(2.55 and 2.32, respectively (p=0.03)]. Both groups demonstrated statistically significant improvement in whole mouth plaque scores throughout the study. However, the test group demonstrated a statistically significantly larger change in whole mouth PI compared to the control group [-1.43 and -0.49, respectively ($p < 0.00001$)].

Modified Gingival Index

Full mouth mean mGI was reported for both the test and control groups at baseline and 3-months.[29] The findings related to mGI at baseline and 3-months are reported in Table 2. At baseline the test dentifrice group had a statistically significant lower whole mouth mean mGI when compared to the control dentifrice group [2.47 and 2.63, respectively (p=0.01)]. Both groups demonstrated statistically significant improvement in whole mouth mGI over the study period, but the test group demonstrated a significantly larger improvement in mGI compared to the control group [-1.11 and -0.16, respectively ($p<0.00001$)].

Modified Sulcular Bleeding Index

Full mouth mean mSBI was reported for both test and control groups at baseline and 3-month evaluations.[30] The findings related to mSBI at baseline and 3-months are reported in Table 2. At baseline the test dentifrice group had a statistically significant lower whole mouth mean mSBI when compared to the control dentifrice group [2.49 and 269, respectively ($p<0.01$)]. Both groups demonstrated significant improvement in whole mouth mSBI over the study period, but the test group demonstrated a significantly larger improvement in mSBI compared to the control group [-1.15 and -0.20, respectively ($p<0.00001$)].

Overall reductions in mean whole mouth PI, mGI, and mSBI were 55.5%, 44.7%, and 46% for the test dentifrice and 20.8%, 5.9%, and 7.5% for the positive control dentifrice (Figure 2). These differences were statistically significantly different for all indices.

Discussion:

Previous studies have evaluated the use of a novel dental gel containing 2.6% EDTA without the addition of fluoride in patients with gingivitis and periodontitis.[22-27,31] Studies evaluating the effects of this dentifrice have demonstrated increased effectiveness of plaque removal, improved gingival health, and diminution of plaque repopulation in patients with gingivitis.[22,31] Further, in Stage I and II periodontitis patients undergoing maintenance therapy after active therapy, the use of the novel 2.6% EDTA dentifrice resulted in statistically significant reductions in periodontal probing depths, plaque index, and gingival inflammation.[25] The mechanism of action of EDTA in plaque and gingivitis reduction has been identified as a reduction in the zeta potential (a measure of electrical charge) on hydroxyapatite spheres more negative, which then resulted in an increased repulsive force between the tooth surface and negatively charged bacteria (unpublished data, available upon request). This increased repulsion further resulted in more facile removal of bacteria from tooth surfaces during toothbrushing and decreased reformation of bacterial plaque biofilm on tooth surfaces. It should be pointed out that this plaque reduction is not based on chemical action, but electrostatic repulsion of bacteria from the tooth surface. An additional study utilizing *in vivo* multiphoton microscopy and digital imaging demonstrated that the reduction in clinical indices associated with the use of 2.6% EDTA dentifrice was correlated with macroscopic fragmentation of the dental plaque biofilm layer.[23] This was contrasted with minimal disruption to the dental pellicle and residual biofilm deposits in individuals who used a positive control dentifrice.[23] Similar to other toothpastes that use calcium chelators as tartar control agents, EDTA usage also results in tartar control. 2.6% EDTA usage in a dentifrice has been shown to be safe for dental enamel.[32,33]

Data also suggest that use of stannous fluoride in a dentifrice has an anti-plaque and anti-gingivitis effect for patients with gingival inflammation.[34-36] Further, in a study with similar baseline whole mouth mean mGI scores, approximately two-thirds of patients using a 0.454% stannous fluoride dentifrice were able to achieve periodontal health (< 10% sites with BOP).[36] However, some of these investigations utilize a negative control[35,37] which may not fully reflect many patients' clinical experiences. Fluoride dentifrice use has also been shown to significantly impact remineralization and reduce caries risk for patients.[38,39] While long-term assessment of caries development was outside of the scope of this investigation, reductions in plaque have been significantly associated with lower dental caries progression in children and adults.[40,41] Although previous studies investigating the novel 2.6% EDTA dental gel demonstrated significant clinical improvements on plaque, leading to associated reductions in gingival inflammation, and periodontal parameters, this is the first study of which the authors are aware evaluating the use of a dentifrice containing both stannous fluoride and 2.6% EDTA as a tartar control agent. The clinical impact of the addition of stannous fluoride to this novel dental gel was unknown prior to this investigation.

The novel test dentifrice utilized in this investigation contained both 2.6% EDTA and 0.454% stannous fluoride. This allows for two distinct mechanisms of action that may have a complementary effect. The EDTA can serve as a chelator and penetrate into the biofilm to alter the availability of positive ions (in particular calcium) and enhance the repulsion between the dental pellicle and biofilm microorganisms.[27,42] The clinical implications of this enhanced negative charge and subsequent increased electrical repulsion include increased biofilm disruption and reduced reformation of biofilm on tooth surfaces. Stannous fluoride has also demonstrated direct antimicrobial properties as well as providing available fluoride ions to form fluorapatite after acidic demineralization of tooth hard tissues.[43,44] This new stannous fluoride formulation may allow for enhanced anti-gingivitis activity as well as improved resistance to demineralization and dental caries formation. Notably, clinically and statistically significant improvements seen in this investigation were similar in overall and percentage reduction to those seen in previous investigations of 2.6% EDTA dental gel in gingivitis patients[22-24] and greater than those seen in treated Stage I and II periodontitis patients undergoing periodontal maintenance.[25] This may indicate that the limit of plaque and gingival inflammation reduction are achieved through the charge repulsion (increased zeta potential) mechanism. It is feasible, however, that the addition of stannous fluoride in combination with lower plaque could impact caries rates for individuals who use the dentifrice, particularly in those with high caries risk. It should also be noted that the test dentifrice does not contain abrasives which are typically found in many commercially available toothpastes and can, over time, cause wear of oral hard and soft tissues. Further, previous studies have demonstrated that the addition of dentifrices to effective toothbrushing does not improve the mechanical plaque removal,[45,46] so this new formulation combines electrostatic repulsion with the stannous fluoride based anti-plaque, anti-gingivitis properties to improve biofilm and gingivitis may represent a substantial paradigm shift in oral home care.

The primary prevention of destructive periodontal diseases require the removal and disruption of dysbiotic biofilm and the subsequent reduction in gingival inflammation seen in patients with gingivitis.[47] It is well-established that gingivitis is, in almost all cases, a necessary precursor to periodontitis.[47] Previous investigations have demonstrated that all individuals are susceptible to develop gingivitis if oral hygiene measures are ceased and that, in patients without established periodontal attachment loss, meticulous oral hygiene can re-establish gingival health.[48,49] Despite the reversible nature of gingivitis, the prevalence of gingivitis in both adults and children is high. Further, while most patients report that they brush twice daily, the reporting of daily interdental cleaning ranges between 1.5-37%.[50,51] Such lower levels of reporting for inderdental cleaning persist despite recommendations from the ADA and other organized dental groups based upon the fact that regular interdental cleaning has been associated with reduced plaque indices and clinical gingival inflammation.[50,51] These findings indicate that adjuvant oral hygiene materials that could allow for significant reduction in plaque levels and gingival inflammation with brushing alone could be impactful in patients who are not currently performing adequate plaque removal and/or those who are at high risk of developing periodontitis.

This study has several strengths, including the documented improvements in both groups, which are similar in scope to those seen in previous investigations of oral care products.[21] Additionally, the use of a control dentifrice allows for assessment of the improved efficacy of the novel test dentifrice as compared to commonly used formulations. Further, the individuals included in this study had a high baseline levels of plaque and gingival inflammation, indicating that they had suboptimal baseline levels of oral hygiene and were at high risk for the development of dental plaque-related dental diseases, including caries and periodontal diseases. This study also did not seek to alter other oral hygiene practices, which likely led to a more real-world implementation of novel dentifrice use that better approximates the behavior patterns of patients, who may be unlikely to substantively change oral home care routines in the long term without ongoing intensive interventions.[52,53] The use of a participant cohort that had a high likelihood of benefit from enhanced oral hygiene efficacy without labor intense behavior modification strategies may allow for immediate integration into oral hygiene recommendations and education practices that are ongoing by dental healthcare professionals.

There are several limitations to the current investigation. While a positive control fluoride dentifrice was used in this study, the fluoride formulation differed from that in the test dentifrice. Therefore, no definitive conclusions can be drawn based upon this investigation about the enhanced efficacy of the bacteria repelling 2.6% EDTA above and beyond that of the stannous fluoride alone. It has been well-established that stannous fluoride demonstrates superior anti-plaque and anti-gingivitis qualities when compared to sodium fluoride.[54-56] Additionally, individuals in this study presented with baseline statistically significant differences in whole mouth mean PI, mGI, and mSBI. To address this, data are reported in both absolute values and in the absolute and percentage change (Δ) for each clinical index. Future studies with a larger sample size may eliminate this possible confounder. Other critiques of this study include the relatively young and healthy nonsmoking patient population, which may have reduced the generalizability of the results for both dentifrices tested when they are used in the general population. Further, this study did not perform baseline periodontal examinations, which then did not allow assessment of changes in periodontal parameters, such as probing depth and clinical attachment level. Given that previous research with a similar dentifrice that did not contain fluoride demonstrated improved probing depth reduction in treated periodontitis patients,[25] future investigations should include such a baseline examination to fully capture any potential additional benefits of this dentifrice. While periodontitis is a prevalent disease in the US population overall, its incidence increases with age so it is unlikely that a substantial number of the young individuals enrolled in this study had significant periodontal attachment loss.[13] Additionally, given the evidence of toothbrush bristle penetration and efficacy of approximately 0.9mm subgingivally, there may be an advantage and/or disadvantage of using the test dentifrice in shallower probing depths associated with gingivitis versus deeper probing depths associated with periodontitis.[57] Lastly, the 3-month study period in this study is insufficient to determine the impact of test dentifrice use on caries rates, but previous studies have demonstrated a correlation between toothbrushing effectiveness and plaque biofilm disruption and decreased caries rates.[38-41,58]

Conclusion:

The results of this clinical study demonstrate that use of a novel dentifrice with 0.454% stannous fluoride resulted in clinically and statistically significant improvements in whole-mouth plaque levels and signs of gingival inflammation when compared to a 0.24% sodium fluoride control dentifrice. This may indicate a benefit for individuals with gingival inflammation and/or suboptimal oral hygiene practices to improve overall oral health. While the baseline clinical indices differed slightly between groups, the directionality and scale of the baseline differences were likely swamped by the overall effect size for the dentifrice. Future studies evaluating the test dentifrice should utilize a stannous fluoride control and consider classifying the overall periodontal health condition to better identify the ideal clinical indications for the use of this dentifrice to prevent and/or reduce the risk of development of dental caries and periodontal diseases.

Acknowledgements:

Conflict of Interest Statement: This study was supported by: LAMMP NIH/NIBIB P41EB05890; NIH/NCI P30CA062203; AFOSR FA95501-17-1-0193; AFOSR FA9550-20-1-0052; the Arnold and Mabel Beckman Foundation through the University of California Irvine; NIH/NIBIB UH2EB022623 through the University of Arizona; and Livionex Inc., Los Gatos, CA. The authors report no conflicts of interest related to this study.

Author Contributions: T. Takesh and A. Goshtasbi contributed to study conception, design, data collection, statistical design, data analysis, and data interpretation; K. Lin, S. Meishan Yang, and C. Wink contributed to clinical observation, execution, and data collection; M. Geisinger contributed to data interpretation, drafted and critically revised the manuscript; P. Wilder-Smith contributed to study conception, design, data collection, statistical design, data analysis, data interpretation, and critical manuscript revision. All authors gave final approval and agreed to be accountable for all aspects of the work to ensure that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

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Figure Legends

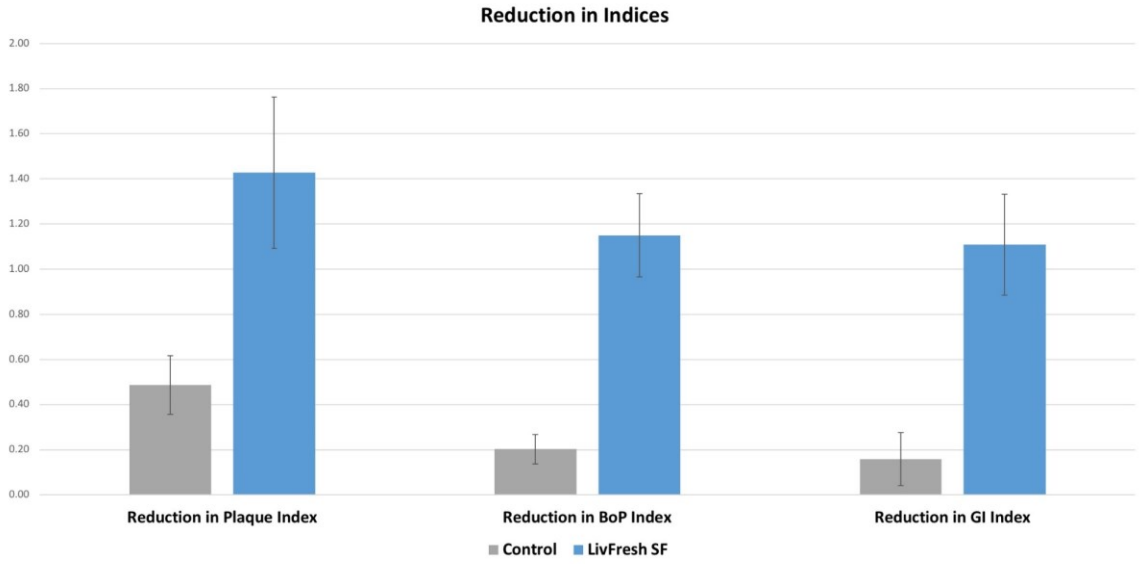

Figure 1: Reduction in clinical indices after 3 months after use of test or control dentifrice.

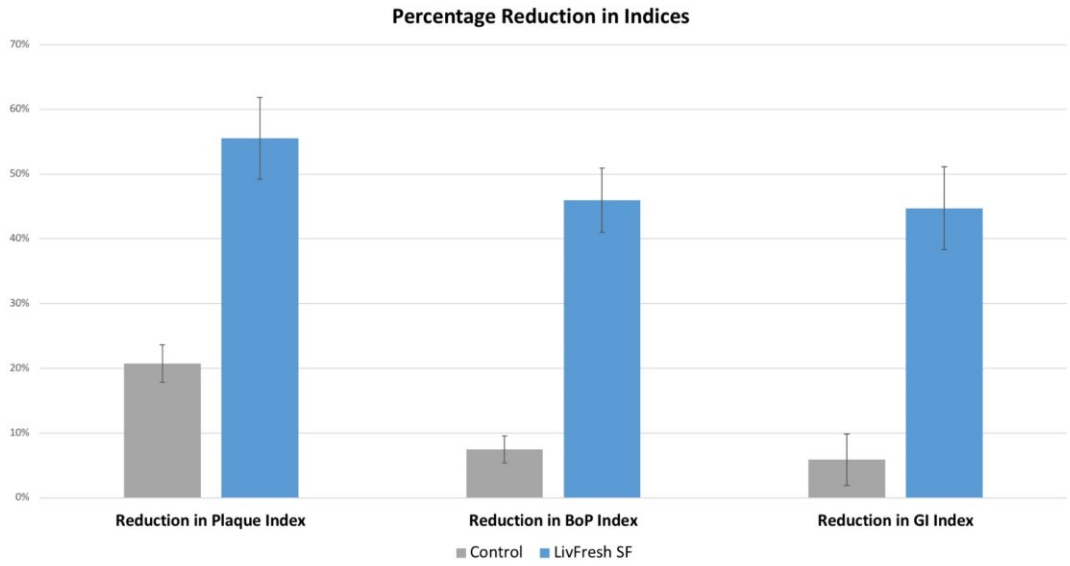

Figure 2: Percentage reduction in clinical indices after 3 months after use of test or control dentifrice.

Table 1: Demographic of participants in test and control groups

	Test (N = 30)	*Control* (N=30)	p-value
Males	14	18	NS
Females	16	12	
Mean Participant Age in Years (Age Range in Years)	22.4 (19-33)	22.7 (19-33)	NS

Table 2: Plaque index changes over the study period for test and control groups

	Mean Whole-Mouth Plaque Index						
	Baseline (SD)	Visit 2 (SD)	p-value	Δ PI (SD)	p-value	% change (SD)	p-value
Control dentifrice	2.32 (0.42)	1.83 (0.30)	< 0.00001	-0.49 (0.13)	< 0.00001	-20.76% (2.89%)	< 0.00001
Test dentifrice	2.55 (0.38)	1.12 (0.14)		-1.43 (0.34)		-55.52% (6.32%)	
	Mean Whole-Mouth Gingival Index						
	Baseline (SD)	Visit 2 (SD)	p-value	Δ GI (SD)	p-value	% change (SD)	p-value
Control dentifrice	2.63 (0.26)	2.47 (0.21)	< 0.00001	-0.16 (0.12)	< 0.00001	-5.88% (3.98%)	< 0.00001
Test dentifrice	2.47 (0.21)	1.36 (0.15)		-1.11 (0.22)		-44.71% (6.42%)	
	Mean Whole-Mouth modified Sulcus Bleeding Index						
	Baseline (SD)	Visit 2 (SD)	p-value	Δ mSBI (SD)	p-value	% change (SD)	p-value
Control dentifrice	2.69 (.19)	2.49 (0.15)	< 0.00001	-0.20 (0.07)	< 0.00001	-7.45% (2.07%)	< 0.00001
Test dentifrice	2.49 (0.19)	1.34 (0.13)		-1.15 (0.18)		-45.96% (4.96%)	